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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,548	12/05/2003	Irving Weissman	STAN-270US2	4320

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EXAMINER	
GAMETT, DANIEL C	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 08/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/729,548	WEISSMAN ET AL.	
	Examiner	Art Unit	
	Daniel C. Gamett, PhD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 17-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-25* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/10/04 8/13/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *IDS: 10/05/2005*.

DETAILED ACTION

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647. The Examiner for this Application is now Daniel C. Gamett.
2. The amendments of 06/26/2006 have been entered in full.
3. Applicant's election without traverse of "FZD cysteine-rich domain (CRD)-lgG fusion protein" in the reply filed on 06/26/2006 is acknowledged. Upon further consideration in view of the specification and Applicant's comments, it is agreed that the more generic term "agent comprising a soluble FZD CRD" adequately distinguishes a single inventive concept that would include "FZD cysteine-rich domain (CRD)-lgG fusion protein" and "frizzled CRD fused to a plasma protein". For purposes of examination, the elected invention may also include the frizzled related polypeptide recited peptides recited in claim 15.
4. Claim 16 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 06/26/2006.
5. Claims 1-15 and 17-25 are under examination insofar as they read upon an agent comprising a soluble FZD CRD or frizzled related peptide.

Claim Objections

6. Claim 1 is objected to because of the following informalities: Apparently a word is missing: "wherein said normal stem cells [are] rendered quiescent." Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 18 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 18 and 21 recite the limitation "said stem cell". There is insufficient antecedent basis for this limitation in the claims.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-15 and 17-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibition of human hematopoietic stem cell (HSC) proliferation by contacting the cells in vitro with an agent comprising a soluble FZD CRD, does not reasonably provide enablement for inducing quiescence in any stem cell by any agent to block extracellular activation of the wnt pathway in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The courts have interpreted the first paragraph of 35 U.S.C. 112 to mean that the specification must

enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

11. *The nature of the invention:* Claim 1 is drawn to a method of inducing quiescence in normal stem cells, the method comprising: contacting said normal stem cells with an effective dose of a protective agent that blocks the extracellular activation of the wnt pathway in said normal stem cells; wherein said normal stem cells [are] rendered quiescent. Claim 17 is drawn to a similar method in which the stem cell is in a patient to be administered a

chemotherapy agent. The term "protective agent" indicates the central premise of the invention, that stem cells can be rendered quiescent by inhibition of wnt signaling, then exposed to anti-proliferative agents without harm, and then return to a proliferative state while retaining multipotency upon relief of wnt inhibition. Claims 18 and 21-25 are drawn to pharmaceutical compositions and kits that include instructions for performing the claimed methods.

12. *The breadth of the claims:* Claims 1, 17, 18, and 20-25 recite any "normal" stem cell and any agent that blocks the extracellular activation of the wnt pathway. Dependent claims variously limit the stem cells or the agent, but no claim limits both the cell and the agent.

13. *The state of the prior art and the predictability or lack thereof in the art:* The finding that HSC proliferation was inhibited by FZD CRD-Ig, even in the absence of added Wnt, is disclosed as a novel finding in the instant specification. The art is silent as to whether the same result would be obtained with other types of stem cell (*e.g.* neural, embryonic, mesenchymal, gut epidermal). The art suggests that not all extracellular inhibitors of wnt, even those structurally similar to frizzled CRD, have identical effects and that not all stem cells will respond in the same way. Secreted frizzled-related protein 1 (SFRP1), which is taught in the instant specification to be an inhibitor of wnt, is equivalent to stromal derived differentiation activity (SDIA), which induces neural differentiation in embryonic stem cells (CA 2467258, page 9, lines 9-11; page 64, lines 13-27; see also CAPLUS Accession Number 2003:397105, Abstract). Therefore, in the case of embryonic stem cells, even if wnt inhibition is indeed accompanied by reduced proliferation or quiescence (unknown), the responding cells would no longer be stem cells.

14. *The amount of direction or guidance present and the presence or absence of working examples:* Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The notion that inhibition of wnt signaling in HSC inhibits proliferation of HSC in vivo is supported by the data shown in figure 3, in which inhibition of wnt signaling was achieved by overexpression of axin, an intracellular negative regulator of the wnt pathway. Thus, the technical problem of achieving an adequate degree of inhibition *in vivo* by using a soluble agent, such as CRD-Ig, was not addressed. The central question of whether cells rendered quiescent by contact with CRD-Ig are protected from anti-proliferative agents was not tested, even *in vitro*. The prophetic guidance provided in Examples 2-4 is directed only to hematopoietic stem cells.

15. *The quantity of experimentation needed:* It would require undue experimentation on the part of the skilled artisan to extrapolate from the enabled scope to include all stem cells and all agents that might be expected to block extracellular activation of the wnt pathway.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C Gamett, Ph.D.,whose telephone number is 571 272 1853. The examiner can normally be reached on M-F, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571 272 0961. The fax phone number for the organization where this application or proceeding is assigned is 571 273 8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DCG
Art Unit 1647
16 August 2006

DAVID S. ROMEO
PRIMARY EXAMINER